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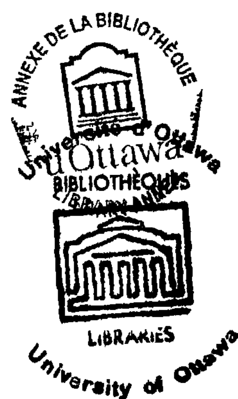
THE EFFECT OF THIORIDAZINE ON HYPERACTIVE CHILDREN AS DETERMINED BY ATTENTION AND MOTOR COORDINATION MEASURES

by Verna-Jean Amell

Thesis presented to the School of Graduate Studies of the University of Ottawa as partial fulfillment of the requirements for the degree of Master of Arts



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CURRICULUM STUDIORUM

Verna-Jean Amell was born April 10, 1952, in Edmonton, Alberta. She received the Bachelor of Arts degree from the University of Alberta in 1974.

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ABSTRACT

For over 25 years stimulants have been the primary drug used in the psychopharmacological management of hyperactivity in children. Recently thioridazine (Mellaril) has been employed as an alternate form of treatment with a small percentage of hyperactive children. The purpose of this study was to determine the effect of thioridazine on span of attention and motor function (two major aspects of the hyperactive pattern) in hyperactive children. Fourteen hyperactive children, ages 5-1/2 - 12 (1 girl, 13 boys), were assigned to Drug and Placebo groups in a double blind manner. They were evaluated with the following attention measures: Digit Span (WISC), Mazes (WISC), Visual Closure (ITPA), Matching Familiar Figures, and Continuous Performance Test. These motor measures were administered: Dynamometer (grip strength), Grooved Pegboard, Finger Tapping, and Coding (WISC). All subjects were evaluated prior to the treatment phase and upon completion of the treatment period. No significant differences were found between the Drug and Placebo groups on measures of attention and motor control, nor did behavioral ratings differentiate between the groups. The findings are discussed with respect to previous research, the methodology, and the efficacy of pragmatic and theoretical research.

INTRODUCTION

In 1937, Bradley reported on the use of amphetamines in the treatment of hyperactive children. Since that time numerous clinical and experimental studies have investigated pharmacotherapy as a primary treatment mode with these children. The majority of investigations have been concerned with the administration of amphetamines and stimulants; however, recently the phenothiazines (and thioridazine in particular) have come under experimental scrutiny. This study is one contribution to the body of knowledge in this regard.

Hyperactivity

In this section, a variety of terms and definitions of hyperactive children is presented. One comprehensive description is discussed at length and adopted for the purpose of this paper.

> The hyperkinetic reaction of childhood is an ill-defined behavior disorder, often of unknown etiology. It is questionable whether the child's activity level is the proper "target" symptom, and it now appears that the hyperactivity may be the result of a more basic disturbance of attention that can be caused by many psychiatric, neurologic, pediatric, and psychological processes (Greenberg et al., 1972, p. 532).

Hyperactivity is a symptom which may be associated with other deficits such as mental retardation, learning disability or minimal brain dysfunction. However, there exists a large group of children for whom hyperactivity is the major

presenting symptom but who do not evidence neural pathology or brain injury. These children are referred to by a variety of terms including "hyperkinetic syndrome" (Millichap et al., 1968; Schnackenburg, 1973), "hyperkinetic reaction of childhood " (Greenberg et al., 1972), and "hyperactive syndrome" (Werry & Sprague et al., 1970). Several authors prefer to refer to these children simply as "hyperactive children" and then describe the accompanying characteristics of the group of children they are concerned with (Gittelman-Klein & Klein, 1975; Weiss, Minde, Douglas et al., 1971).

Safer and Allen (1976) have discussed the rationale involved in this latter position. They define hyperactivity as a developmental disorder characterized by a long-term pattern of excessive restlessness and inattentiveness.

They refer to hyperactivity as a developmental "pattern" because the term "hyperactive" is limited in scope.

> Hyperactive children have no more total daily body activity than non-hyperactive children. However ... they have difficulty modulating their activity level, particularly when they are expected to perform an abstract academic task (Safer & Allen, 1976, p. 6).

The term "hyperactivity" is then more meaningful when viewed from the perspective of a persistent developmental pattern.

Safer and Allen also suggest that the term "syndrome" has a limited applicability because it implies a set of co-existing characteristics.

> The clinical signs and symptoms of developmental hyperactivity, however, have only a modest degree of inherent unity, not enough at this time to technically merit the tag "syndrome" (Safer & Allen, 1976, p. 6).

The concept of a developmental hyperactive pattern (as outlined by Safer & Allen) will be adopted for the purpose of this paper since it most adequately describes the children who participated in this investigation.

What, then, are the characteristic features of the hyperactive (HA) pattern?

The only necessary feature of the HA pattern is developmental hyperactivity evident in "the persistent pattern of excessive activity in situations requiring motor inhibition" (Safer & Allen, 1976, p. 7).

However, there are four prominent characteristics which are commonly associated with HA. These include inattentiveness (the inability to maintain attention); a learning impediment (evidenced in an academic lag and difficulty grasping abstractions); behavior problems, i.e., misconduct; and immaturity, reflected in part in their difficulty in coping with environmental changes (Safer & Allen, 1976).

A number of other emotional and behavioral features occur fairly often in HA children. Impulsivity is quite common and has been discussed at length in a review by Ross and Ross (1976). They cite the position of Kagan and Messer (1975) who find the assessment of cognitive styles--on a

reflective impulsive dimension--valuable in differentiating between children. Douglas and her associates at McGill support Kagan's position, but suggest further that the problems of attention and impulse control are reciprocal aspects of the same process. They suggest that many of the school difficulties of the HA child may be attributed to his inefficient cognitive styles.

Peer difficulties associated with the HA child's emotional reactivity, explosive irritability, and aggressiveness are frequent (Berman & McKinney, 1973; Kornetsky, 1970; Safer & Allen, 1976).

Another important characteristic which distinguishes HA children from other clinical groups is that their intellectual ability is generally unimpaired.

What is the prevalence of HA, and how are these children distinguished from their peers for treatment?

Safer and Allen (1976) estimate the prevalence of HA to be approximately 8 - 9% in elementary school boys and 2 - 3% in elementary school girls. In child guidance clinics, 30 - 40% of the children who are evaluated have HA. HA has been referred to as the most common psychiatric disability of childhood.

Children may be distinguished as HA by their physicians through a detailed history which indicates the features previously discussed; and by parents and teachers with the aid

of the Conners Rating Scale (Conners, 1970). This is a 96-item behavioral checklist[1] which is marked on a continuum from "not at all" to "very much." Werry and Sprague (1974) found that HA children scored 2.9, 2.0, 0.9, and 3.4 standard deviations from the mean on the rating scale in factors of conduct problem, inattentiveness, tension, and hyperactivity, respectively. This indicates that HA children are clearly distinguished from normal children in factors of hyperactivity and conduct problems. They also found the teacher ratings to be the most stable source of information for assessing drug effect (methylphenidate vs. placebo).

In sum, HA children are distinguished from normal children primarily with respect to their activity level, attentional processes, conduct, and learning impediment.

Considering the nature of the difficulties experienced by the HA child, there have been various methods and approaches to treatment (1, 21, 64, 66). Operant control of attention behavior has been proposed as a meaningful supplement to drug therapy; two cups of coffee a day or substituting caffeine for stimulant drugs has also been recommended. A comprehensive program with behavior modification, pharmacotherapy, curriculum counseling, training for parents and teachers accompanied by parent-child interaction videotaping

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1 An abbreviated 10-item questionnaire is also available.

and feedback sessions has been devised by Feighner and Feighner (1974). The treatments employed with HA children range from using stimulants and tranquilizers, corticosteroids, antihistamines, anticonvulsants, food elimination, air filtration, allergic desensitization, to perceptuo-motor training and behavioral counseling (64, 66).

The variety of treatments reflect the variety of etiological theories regarding HA. They range from organic factors such as brain damage incurred by perinatal complications, to child rearing, to environmental factors including food additives (Feingold), lead poisoning, radiation stress, maternal smoking, and living in overcrowded slums (41).

There have been several theoretical formulations of brain dysfunction as an etiological factor in HA based on models that emphasize the interaction of excitatory and inhibitory systems within the central nervous system. This theory arose as an attempt to explain the "paradoxical" effect of the stimulant medication on HA children. Briefly, the theory (as discussed by Wender and Sroufe [41]) is that over-aroused children become quieter and normal children become over-aroused with a subsequent deterioration in performance as a function of moderate doses of stimulant medication. At present there is insufficient empirical evidence to confirm this theory. For a more detailed discussion of the metabolization at the neurotransmitter level, see Ross and Ross, 1976, p. 71-72.

Though all the aforementioned treatment methods are possible, the treatment modality most frequently employed with HA children is psychoactive medication designed to improve attention span, cognition and learning, and to decrease hyperactive behavior.

Psychopharmacological Management of Hyperactivity

In 1973, 1.73% of the children in schools surveyed in Baltimore Country, Maryland, were on medication and of these 88.2% were receiving stimulants, either methylphenidate (Ritalin) or dextroamphetamine (Dexedrine) (Krager & Safer, 1974).

Amphetamines and stimulants have been used extensively in the pharmacotherapy of hyperactive children (7, 13, 26, 29, 35, 36, 38, 41, 64, 66); the general conclusions and findings will be discussed here. For a more comprehensive review of this aspect of hyperactivity there are several excellent reviews, specifically Kornetsky, 1970; Lambert et al., 1976; Ross and Ross, 1976; and Vol. 4 of The International Journal of Mental Health, 1975, which deals solely with the topic of hyperactivity.

The effect which stimulants and other drugs have on HA children has been evaluated in regard to a number of aspects of the HA pattern. These include: psychological evaluations--attention span, concentration, impulsivity,

cognitive and learning abilities; behavioral ratings; physiological responsiveness--EEGs, blood tests; motor behavior--seat movements, grip strength, finger tapping; physical characteristics--growth over extended periods of drug administration; and clinical evaluations of individual differences in temperament, social interaction, and responses to medication, i.e., side effects, maximum dosage for therapeutic effect, etc.

Of primary concern for many investigators is the effect of medication on the attentional processes. This is evaluated with tasks that measure components of attention such as temporal and selective attending, and indices of attention such as reaction time.

> The temporal component of attention is the ability to respond consistently and it is an attention-span or duration of attention skill that can be measured on vigilance tasks such as continuous performance tasks.[2] The selective component is an information-processing skill that involves the ability to focus on the relevant or central aspect of a task and to exclude the irrelevant or peripheral aspects (Ross & Ross, 1976, p. 144).

Sykes, Douglas, Weiss and Minde (1971) employed the Continuous Performance Task (CPT) and found that HA children detected fewer signal stimuli and made more incorrect responses to nonsignal stimuli. However, HA subjects taking

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2 In this task a series of letters are projected one at a time on a screen. The subject is required to monitor the screen and respond whenever a specified stimulus (the signal stimulus) appears.

methylphenidate improved their performance, compared to a placebo control group. Sykes, Douglas and Morgenstern (1972) chose four tasks (two reaction time [RT] tasks, and a visual and an auditory presentation of the CPT) and found methylphenidate improved performance on all measures. Sprague, Barnes and Werry (1970) devised a task involving picture recognition of stimuli in which the subject was to determine whether the test stimuli was in a previous presentation or not. The authors noted an improved performance when the children were receiving methylphenidate. Werry and Aman (1975) employed the same task to compare the effects of methylphenidate and haloperidol; at reasonable dosages they facilitated performance, but at high doses haloperidol caused a deterioration in performance.

Weiss, Minde, Douglas, Werry and Sykes (1971) compared chlorpromazine, dextroamphetamine, and methylphenidate and found that, compared to placebo, all drugs produced an overall behavioral improvement. However, methylphenidate was the most effective in producing more goal-oriented behavior and reducing distractibility (the shifting of attention). With respect to cognitive functions, chlorpromazine was indistinguishable from placebo. Both stimulants produced improvement in some of the tests; however,

> no firm conclusions could be drawn as to specific functions altered, and there is no definite evidence at present that perception, fine motor

> control or perceptuo-motor functions are significantly altered by the drugs (Weiss et al., 1971, p. 24).

The authors suggest that their findings may be explained as spurious improvements resulting from the effect of the stimulants on attention. Final conclusions, they caution, are unwarranted.

In a review by Conners (1971), he suggests that the available evidence indicates that stimulants (particularly methylphenidate) are superior to phenothiazines (particularly thioridazine) on learning tasks due to the enhanced attention to the task and/or increased arousal levels or motivation; and further, that the HA children are impaired in their ability to plan and attend by the phenothiazines. These comments will be reconsidered in the section dealing with the phenothiazines and their application to HA children.

Knights and Viets (1975) reported on a long-acting stimulant--magnesium pemoline (Cylert). They employed a battery of standardized psychological tests and performed 28 analyses of variance on total scores for each test and on the subtests of the WISC and WRAT.[3] There was no differential effect of the drug on any of the psychological measures. However, behavior ratings by teachers and parents indicated

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3 Wechsler Intelligence Scale for Children, 11 subtests; Wide Range Achievement Test, 3 subtests.

an improvement in HA problem behaviors related to distractibility, impulsivity, and attention span.

Gittelman-Klein and Klein (1975) investigated the relationship between psychometric and behavioral changes resulting from the administration of methylphenidate to HA children. They did not find any meaningful patterns of related change between behavioral and cognitive indices. The authors state:

> The notion that a primary unitary, CNS function is ameliorated by stimulants, leading to a remission of many secondary symptoms, seems unlikely on the basis of our findings. Drug effects in this population appear more complex (p. 195).

Although a significant "clinical" drug effect was demonstrated within four weeks of methylphenidate treatment, relatively few positive psychometric changes occurred.

Behavioral ratings have been quite valuable in the clinical evaluation of the effect of medication on HA children. Sprague, Barnes and Werry (1970) found that stimulant drugs reduced inattentive behavior, undirected motor behavior, and number of punishments received for disruptive behavior, in the classroom situation. And that stimulants tend to increase both the child's attention to learning tasks and the amount of positive teacher contact with the pupils. Weiss, Minde, Douglas, Werry and Sykes (1971) found that while the _quantity_ of activity (as detected by mechanical devices) was not altered by stimulant medication, the _quality_ of activity

(more goal-directed behavior) was such that parents and teachers considered the overall activity of the child to have decreased. Teachers' ratings are considered by several investigators to be a reliable sensitive measure of drug effects. This was evident in a study by Knights and Viets (1975) who found that teacher ratings demonstrated only a slight placebo effect and showed greater differentiation between the drug and placebo groups.

Safer and Allen (1975) evaluated 38 HA children who were treated with stimulants during the years 1967-1974. Between 1969 and 1971 Dexedrine (dextroamphetamine) was prescribed preferentially, but after 1971 Ritalin (methylphenidate) was used almost exclusively. Eleven behaviors of a teacher behavior checklist were sorted into three major aspects of the HA pattern: hyperactivity, inattentiveness, and aggressive misconduct. The major findings were that the therapeutic response did not significantly change from age 6 to age 16. As a group, before treatment, teenage HA children were as inattentive as younger children, but less aggressive and overactive. Parental resistance to the stimulants was not related to the age of the child but behavioral resistance by the child increased significantly during the teens.

In a review by Wiens (1972) of studies on behavior modifying drugs used with HA children, 20 studies showed

objective behavioral change as a function of drug therapy, but 57 reported no significant differences. However, when subjective measures were used, there was a preponderance of positive significant results (86 of 133 studies surveyed). This study demonstrates the need to determine that the raters (parents & teachers) have a common understanding of what is referred to in each statement of the checklist and what is considered "very little" or "excessive" activity.

Physiological indices have been employed for the purpose of exploring the theoretical propositions regarding the mechanism of action of medications. Monitoring the EEGs when a child is receiving stimulant medication has shed some light on the hypothesis of the paradoxical action of these drugs (see Kornetsky, 1970, pp. 128-129). At present, however, this "meta-neuropharmacology"--as Kornetsky calls it--is somewhat unsatisfactory. It is one attempt, however, to come to terms with the findings of the behavioral and neuropharmacological studies.

Only recently has concern been expressed regarding the long-term physiological consequences of stimulant drug intervention. One example of this is a study reported by Safer and Allen (1975) where children receiving Dexedrine or Ritalin failed to achieve expected gains in height and weight during a 3-year period. There has also been some concern regarding the potential abuse of stimulant medication

by the children, and by parents and teachers who erroneously conclude that if one pill helps two will be even better. The prevalence of abuse is not known, however, and few empirical studies deal directly with this matter.

To summarize the foregoing discussion, it is evident that the stimulants are helpful in improving attention, that the quality of behavior as rated by parents and teachers is improved, that motor behavior is unaffected, and that evidence on cognitive perceptuo-motor functions is inconclusive.

What contributions have the phenothiazines made to the psychopharmacological management of HA, and why are they employed when the stimulants have such a well-documented history of use?

The next section will address itself to these questions and briefly outline the history of the phenothiazines and their emergence in pediatric psychopharmacology. This will be followed by a discussion of the properties of phenothiazines and thioridazine in particular.

Phenothiazine

Phenothiazine was synthesized in 1883; in the late 1930s a derivative of phenothiazine (promethazine) was found to have antihistaminic properties and a strong sedative effect. In 1950, promethazine was tried in the treatment of motor agitation in mental disease but without much success.

The same year the French surgeon, Laborit, introduced the drug as a potentiating agent in clinical anesthesia. This prompted a search for other phenothiazine derivatives with potentiating actions and within the year Charpentier synthesized chlorpromazine. In 1952, Courvoisier and her associates described an amazingly large number of actions manifested by chlorpromazine. The first report on the treatment of mental illness by chlorpromazine alone was made by Delay and associates (1952). In 1954, Lehmann and Hanrahan reported on the use of chlorpromazine in the treatment of psychomotor excitement and manic states. Clinical studies soon revealed that the most important action, as well as the most widespread usefulness of chlorpromazine, was in the treatment of psychotic states, and it has since been used primarily for psychiatric purposes (25).

Following the introduction of chlorpromazine, many other phenothiazine derivatives were developed and, although therapeutically they appeared similar, each presented demonstrable differences. Thioridazine[4] has proved to have a broad spectrum of useful activity and is considered by many to be a good all-round tranquilizer. Initial investigations of thioridazine in the treatment of behavior disorders in children appeared to indicate a valuable addition to the armamentarium

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4 Mellaril (Sandoz Pharmaceuticals).

of drugs available for this condition (see Alexandris & Lundell, 1968). Thioridazine is now the most frequent alternative to stimulant medication for HA children. Safer and Allen (1976) indicate that 5 - 10% of HA children on drugs for their behavior receive either thioridazine or, less frequently, chlorpromazine. These medications have the effect of lessening restlessness and quelling anxiety. They have been found to be especially beneficial with HA children who are psychotic or mentally subnormal. However, thioridazine has been employed primarily in controlling aggressive, hyperactive behavior. For the typical HA child thioridazine has been found to be more effective than placebo but not as beneficial as the stimulants. (This will be discussed further in a subsequent section on the applications of thioridazine in treating HA.) Stimulants, then, are the initial drug of choice with thioridazine as the alternate drug, especially for that group of HA children with conduct problems and the few children who do not respond to the stimulants.

What effect does thioridazine have and what is its mechanism of action? The next section deals with the properties of the phenothiazines and thioridazine, in particular.

There are three major subgroupings of phenothiazines: (1) the sedating phenothiazines of which chlorpromazine is a member; (2) the piperazine ring phenothiazines--which have

a common effect of stimulation and are represented by trifluoperazine; and (3) the piperidine phenothiazines which are considered neither depressing nor stimulating allegedly causing fewer Parkinson-type side effects. The major representative of this latter group is thioridazine[5] and it is the only drug in this subgroup reported on in the child literature.

In a review of studies which investigated the effectiveness of standard phenothiazine derivatives, J. Davis (1970) (see Clark & del Giudice, 1970) showed that the derivatives are approximately equal in therapeutic efficacy. Thioridazine, for example, is equipotent with chlorpromazine but fewer side effects are reported. (Common side effects for phenothiazines include extrapyramidal symptoms--Parkinsonism, lethargy, dry mouth, blurred vision, constipation, and weight gain.) The primary danger with thioridazine is that in doses over 1000 mg/day it can produce pigmentary retinopathy. Most of the mild side effects seen in adult use such as drowsiness,[6] constipation, skin reactions, etc., are seen in children but less frequently than might be expected considering the higher

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5 See Appendix 1 for chemical structure.

6 Tolerance to the soporific effects of phenothiazines develops rapidly so that dosage reduction is unnecessary.

milligrams of drug per kilogram of body weight usually utilized (Clark & del Giudice, 1970).

Thioridazine differs from the other phenothiazines pharmacologically in that it is a potent adrenergic blocking agent. It acts by blocking the uptake of epinephrine (adrenaline) in the autonomic nervous system thereby inhibiting some activities of the sympathetic nervous system which include acceleration of heart beat, elevation in blood pressure, and other bodily changes necessary to prepare the body for emergency conditions.

> The action of phenothiazine drugs in the hyperkinetic child are well within the spectrum of effects of this class of compounds. The enigma of the central nervous system stimulant effects in the hyperkinetic child is unresolved (Kornetsky, 1970, p. 128).

Applications and Research with Thioridazine

What is the clinical effect of thioridazine on HA children? In what areas does it induce improvement?

Comparative Studies

Werry (1968) (see Kornetsky, 1970), in a review of HA in children, concluded that only two types of drugs are useful with these children--methylphenidate and the phenothiazines. He indicated that the effect of the phenothiazine is more predictable in slowing down the hyperkinetic child; however, the quality of the response is not as good as is

found with the use of methylphenidate. Werry et al. (1966) reported that chlorpromazine was significantly superior to placebo in reducing hyperactivity. On a vigilance task, however, the drug subjects performed better than the placebo subjects but the difference was not statistically significant (Kornetsky, 1970). Freibergs et al. (1968) found that moderate doses of chlorpromazine over relatively short periods can be successful in reducing hyperactivity in children, without apparently affecting learning ability and other psychological functions.

Alexandris and Lundell (1968) compared thioridazine, amphetamine, and placebo in low IQ hyperactive children. They employed a number of subtests from a standardized intelligence test and found thioridazine to be more effective than amphetamine in improving scores. Abbott et al. (1965) found thioridazine useful with mental retardates in that the "tranquilizing" effect served to reduce assaultive behavior, hyperactivity, and temper tantrums. Unfortunately, this study lacked a control group and the evaluation was a subjective rating by ward staff.

Davis (1971) investigated the effect of thioridazine and methylphenidate on the stereotyped behaviors of retarded children. The results suggest there were individual but not group effects. Davis, Sprague and Werry (1969) had previously demonstrated in a group of retarded children that

thioridazine had significantly decreased stereotypic behavior without affecting other behaviors but also reported a large proportion of variance due to individual responses to drugs.

Greenberg et al. (1972) compared dextroamphetamine, chlorpromazine, and hydroxyzine to placebo and failed to find significant effects with respect to standard psychometric measures, but they report "favorable" effects on these measures compared to placebo.

Sprague, Barnes and Werry (1970) compared methylphenidate and thioridazine and found that the reaction time of subjects on thioridazine was slower due to the characteristic effect of drowsiness and general decrease of arousal. They also indicate that previous research on thioridazine in regard to nondirected overactivity of HA children has been contradictory and inconclusive.

Alderton and Hoddinott (1964) reviewed studies on the use of thioridazine and discovered few that were objective and controlled. They conducted a double-blind study and found thioridazine to be a safe and useful drug in the treatment of hyperactive, aggressive, destructive patterns of behavior in children.

Werry et al. (1970) compiled the data they had accumulated in their Illinois studies as well as the data from their Montreal group and came to the following conclusions regarding the phenothiazines (chlorpromazine & thioridazine).

In the clinical (or naturalistic) setting they found (1) no consistent effect on attention in the home or classroom; (2) HA, aggressive children were perceived as improved by their mothers but less clearly so by teachers (global ratings showed an improvement but the changes were not significant); (3) inappropriate motor behavior (hyperactivity) was reduced as perceived by mothers, however, the effect in other settings (i.e., classrooms) was inconsistent for motor behavior and deviant behavior of all kinds; and (4) positive teacher-pupil interaction was reduced.

In the laboratory or one-to-one situation they found (1) an increase in the latency of responding; (2) a deterioration of task performance under certain conditions, i.e., where the task is a simple repetitive motor task and where the level of task difficulty is optimal; and (3) no consistent effect on motor activity as measured directly by mechanical or electronic means.

The correlation between the laboratory and clinical studies is not good. The laboratory studies tend to show a slight deterioration of performance, while the clinical studies show a more mixed effect with improvement exceeding impairment. This is understandable in that the laboratory studies are concerned chiefly with cognitive functions, and the clinical with behavior. The phenothiazines depress central nervous system function, affecting cognition and behavior. The

behavior is consequently seen as improved because activity has been reduced, while cognitive functions become impaired due to the depressive effect of the drug.

In studies by Werry et al. (1970) which compared the phenothiazines to the stimulants, the phenothiazines were found to be inferior in effect on behavior and cognitive function. The relationship of the phenothiazines to placebo was less clear in that the majority of differences did not achieve statistical significance.

Gittelman-Klein and Klein et al. (1975) also conducted extensive investigations of phenothiazines (particularly thioridazine) and stimulants (methylphenidate) in the treatment of HA children. They found that both drugs decreased motor activity, however with stimulant medication the children were less sedated, more alert, and concentrated better. With thioridazine, significant side effects were frequent at high doses (300 mg/day), while lower doses did not induce satisfactory therapeutic responses. Children whose level of activity and impulsivity improved, frequently failed to show the lasting improvement in social and academic functioning which had been found with the stimulants.

The most common side effect with thioridazine was drowsiness and difficulty in being aroused. This diminished with time, but did not disappear. A large number of the children developed enuresis, increased appetite, and significant

weight gain. The most significant symptom in children maintained on thioridazine for more than two months was a slow deterioration in mood and behavior--their activity level would remain satisfactory. Gittelman-Klein et al. recommend combining thioridazine and methylphenidate in two situations: (1) in children inadequately controlled on stimulants and for whom the stimulant dosage cannot be increased due to side effects, they suggest 25-150 mg/day of thioridazine be given in addition to the stimulant dose; and (2) in children who experience severe sleep disturbance and loss of appetite on the stimulants (and who would lose the clinical effect if the stimulant were reduced) add thioridazine 25-100 mg/h.s. (before bed).

The authors are recommending thioridazine as a soporific agent and tranquilizer. In children in whom such combinations are introduced, judicious observation and evaluation are necessary. (No other studies to date have recommended that these drugs be combined in treating HA. The usefulness and theoretical soundness of such a recommendation is questionable.)

In a review by Conners (1971), he states that HA children are "generally impaired" in their planning ability on the Porteus Maze Test, and on vigilance tasks measuring attention and impulsiveness, by the phenothiazines. This statement follows from a discussion of the improvement found in these areas with the stimulants. It is not clear whether

the phenothiazine "impairment" is in comparison to a baseline behavior, to a placebo, or a direct comparison to the stimulants. (One expects the stimulant to "outperform" the phenothiazine. However, one does not erroneously conclude that the phenothiazine is then "impairing" any function.) It does not appear to be a significant impairment or it would have been expressed as such. At present it is best to hold these conclusions in abeyance as other studies (previously discussed) find either no difference between placebo and phenothiazines or inconclusive evidence as to their effect.

The difficulty in evaluating the meaningfulness of Conner's statement leads to an important issue in considering the psychopharmacological impact of any drug--the methodology involved in the investigation.

Methodology of Psychopharmacological Studies

Sprague and Werry (1971) outline six criteria which they consider to be the minimum requirements necessary for a sound psychopharmacological investigation. They are: (1) placebo control, (2) random assignment of subjects, (3) double blind, (4) standardized dosages, (5) standardized evaluations, and (6) appropriate statistical analysis.

As well as having a placebo control, it may also be preferable to have a no-drug condition to assess the placebo effect. Random assignment of subjects is necessary to eliminate

bias in the sample, and if a matched-pair design is used members of the pair should be assigned at random to the conditions. In a crossover design (where each subject receives each experimental condition), the subjects should be randomly assigned to the sequences of treatment used. Random assignment is necessary to meet the minimum assumptions of the statistical tests used. To prevent the investigators' expectations from influencing the assessment of the subjects' behavior, neither the subject nor experimenter should have knowledge of which is the placebo or active medication condition--this is the double-blind requirement. At present, in most studies, the drug dosage varies throughout the study for individual subjects. It is desirable to standardize the dosage on a mg/kg (milligram per kilogram of body weight) basis, to allow comparisons across investigations.

In discussing standardized evaluations, Werry and Sprague recommend that the measuring device have been in use, and that there be empirical information on basic reliability and validity. (That the instrument gives the same finding when repeated across testers and/or time and that there is independent evidence that the instrument is actually measuring what it purports to measure.)

The most acceptable manner of data evaluation is to use inferential statistics; one should ensure that the statistic is appropriate and that basic assumptions of the test have not been violated.

Fish (1969) suggests further that descriptive characteristics of subjects can establish common reference points and that these "pre-treatment conditions" be defined in operational terms and accounted for in the design of the experiment. (This is a further refinement of the practice involved either in matching subjects or random assignment to conditions.)

Another matter of importance in any drug study, which is related to the requirement of standardized drugs, is that of period of drug administration. It is generally accepted that six weeks is the necessary period required to properly evaluate drug effects. Evaluations made prior to this time may not be illustrative of the "therapeutic effect" which is possible with the drug.

Knights and Viets (1975) recommend that when small samples are used that "data obtained for subject selection be reviewed prior to group assignment and that a matching procedure be used rather than blind and random placement of subjects into groups (p. 1113). This followed from a study they conducted in which they found that the Placebo group had an initial mean Full Scale IQ of eight points lower than the Drug group. They question whether this may have confounded the results re drug effects. Another important point which they raise in regard to finding group differences on psychological tests in drug studies is the ratio of the number of test

variables that are significant, compared to the number of variables on which significance tests were conducted. They suggest that, "looking at data as a percentage of significance obtained over the many analyses conducted is a more conservative interpretation of the results" (p. 1113).

How many investigations meet these requirements? Sprague and Werry (1971) reviewed 16 studies conducted in a 10-year period (1960-1970) which had investigated thioridazine. Of these, six met the minimum requirements. Among these six, all had significant results; three of the studies evaluated "learning, activity," one evaluated marble dropping, one used a developed scale and the WISC Test, and the other used an activity index. (All of these studies were conducted with mentally retarded subjects.)

Alexandris and Lundell (1968) conducted one of the best methodological studies (according to Sprague & Werry) investigating the effects of amphetamine and thioridazine on retarded children. Using the Duncan Range Test to evaluate the difference between pre- and posttest scores they found thioridazine superior to amphetamine on concentration, aggressiveness, sociability, interpersonal relationships, comprehension, work interest, and work capacity, with thioridazine superior to placebo on all these items plus four others; and with amphetamine superior to placebo on comprehension and work interest. There were no significant differences on psychological test (WSIC) change scores.

Does meeting all the methodological requirements ensure that the effect produced can be attributed to the drug administered? Or can it be simply attributed to a physiological change of state of the organism, and not to any particular aspect of the drug in question?

State Dependence

Aman and Sprague (1974) addressed themselves to this question, evaluating methylphenidate and dextroamphetamine on learning and retention tasks. They employed a recognition task, a paired associate task, and a maze task. Neither drug significantly improved learning or retention performance and, although numerous dependent measures were used for each task, all tests for state-dependent effects were nonsignificant. What this means is that the successful performance of the learning tasks did not depend on a change of state in the HA child induced by the stimulant.

Swanson and Kinsbourne (1976) conducted a study of state-dependent effects with stimulants and found that "when the drug treatment is initially ineffective in establishing an altered state, state-dependent effects are not demonstrable" (p. 1356). They indicate that this explains the results which Aman and Sprague found--because the initial drug treatment failed to show a behavioral (learning) difference in state, no change of state was necessary for retention

performance. Swanson and Kinsbourne conclude that:

> state dependency, then, is conditional on there being the same drug effect on behavior during acquisition as during retention, which presumably depends on an effective drug treatment (p. 1356).

In their study, they demonstrated a state-dependent effect in that the stimulants facilitated performance on learning tasks.

One cannot extrapolate from these findings to the phenothiazines, but it cautions one to carefully evaluate any study which finds a strong effect in every task measured. When no discriminating effect is measured, it can be suspected that no discriminating effect exists, and that the results are as easily understood in terms of a general change of state of the organism, not attributable to any specific function of the drug in question.

What tasks are used to evaluate drug effects and how objective are they?

Psychological Tests and Measures

Many studies have employed psychological tests and measures to obtain objective data in order to evaluate the effects of various drugs on hyperactivity (Alexandris & Lundell, 1968; Ault et al., 1972; Berman & McKinney, 1973; Gradbard, 1974; Butter & Lapierre, 1974, 1975; Cunningham, 1974; Gittelman-Klein & Klein, 1975; Hartman, 1973; Klein,

1975; Krippner et al., 1974; Millichap et al., 1968; Schnackenberg & Bender, 1971; Seger & Hallum, 1974: Tarver & Hallahan, 1974). Tests have included: Burdock's Children Behavior Rating Scale; Benton Visual Retention Test; Good-enough Intelligence Test; Wechsler Intelligence Scale for Children (WISC); Bender Gestalt Visual-Motor Test; Peabody Picture Vocabulary Test; Memory-for-Designs; Raven Progressive Matrices; Wide Range Achievement Test (WRAT); Frostig Developmental Test of Visual Perception; Lincoln-Oseretsky Schedule of Motor Development; Porteus Mazes; and subtests of the Illinois Test of Psycholinguistic Ability (ITPA). Various neuropsychological tests have also been employed, as well as measures of attention using the Continuous Performance Test (CPT). Other tests include: motor activity measures--wrist watch actometer; motor coordination--finger tapping; visual-motor perception--Bender Gestalt and Frostig; the auditory subtest of the Detroit; a general test of intelligence using Draw-a-Man; and conduct, personality and immaturity measured with the Peterson-Quay scale (Millichap et al., 1968).

Results of these studies usually report "beneficial" but not significant results when comparing the drug and placebo groups.

However, valuable information regarding the nature of hyperactivity and some specific effects of drugs has been

obtained in studies using objective psychological measures.

A review by Sroufe and Stewart (1973) of studies employing stimulant drugs suggests that drug-treated HA children perform better than placebo controls on certain subtests of standard IQ tests (i.e., coding and digit span on the WISC); maze tracing and figure drawing; achievement tests; paired associate learning tasks and portions of the Frostig. On vigilance tasks such as the CPT, fewer errors of omission and comission occur in the stimulant group and reaction time (RT) is faster. Matching to standard, and delayed recognition are also improved. Reaction time and RT variability are reduced by stimulant drugs. The few long-range studies conducted suggest that drug treatment effects are modest at best.

The Matching Familiar Figures (MFF) test is used to measure reflectivity-impulsivity. HA children made more errors and had significantly shorter response latencies on the MFF, suggesting a positive relationship between hyperactivity and impulsivity (Tarver & Hallahan, 1974). Ault et al. (1972) classified children in a third-grade classroom according to their MFF scores. They then had the teachers rate the children on factors of hyperactivity and attention. They found that "boys are seen by their teachers as hyperactive regardless of their MFF classification, while only

reflective subjects of either sex are rated highly attentive" (p. 1417). This suggests that caution be exercised in applying teachers' ratings as a diagnostic criterion and that results of the MFF may yield finer differentiation among children than is obtainable with teacher ratings alone.

HA children detect fewer embedded figures than controls (Tarver & Hallahan, 1974). This finding was investigated by Butter and Lapierre (1974, 1975) who examined perceptual deficiencies of HA children and the effect of methylphenidate using subtests of the ITPA. The nonverbal subtests included auditory reception and memory--which test the ability to comprehend and attend to the spoken word; visual reception--the ability to comprehend pictures and written words; visual closure--picture identification selecting embedded figures from an irrelevant background; and manual expression. The only improvement with the stimulant was in the auditory modality.

Using a battery of cognitive tests (WISC, WRAT, etc.), Cunningham (1974) demonstrated a significant improvement in these areas with HA children taking calming drugs.[7] There were insignificant losses in the stimulant drug group in these same areas, and no change in the no-drug group. Length

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7 There is no indication as to the identity of the "calming drug," see Dissertation Abstracts International (1974).

of time on the drug seemed to have an effect, as subjects on the calming drug for a period of 2 - 5 years performed better than subjects on the same drug for 6 - 10 years. Subjects on stimulant drugs also showed poorer performance the longer the time on the drug.

Bradbard (1974) found improvements in the cognitive area when HA children were given methylphenidate. She also used the WISC and WRAT as well as the Porteus Maze Test and other psychological tests. The evaluation of performance was made using the Porteus Maze Test and teachers' global ratings of academic achievement.

The method of investigation in these two studies is questionable. Global measures, which are affected by a number of factors (difficult to control) and represent a number of cognitive functions, are the indices of evaluation. The results obtained cannot be as simply interpreted as the authors suggest. Secondly, the pretest and posttest evaluations differed in terms of number of measures taken and types of measures employed. The importance of these studies is that investigators are becoming increasingly concerned with the effect of drugs on cognitive functions, and are attempting to evaluate these effects with traditional measures.

Berman and McKinney (1973) established a factor structure of the WISC for HA children. This may aid future investigators in refining the psychological measures they

choose to employ in drug study evaluations. Traditionally, Wechsler variance has been consistently accounted for by three to four factors: verbal comprehension, perceptual organization, memory, and a fourth factor usually termed a general factor. The factor structure which developed when the scale scores of HA children on the 11 subtests of the WISC were analyzed was as follows: Factor 1 = verbal comprehension--Information, Comprehension, Arithmetic, Similarities, Vocabulary, and Picture Arrangement; Factor 2 = perceptual organization--Picture Completion, Block Design, Object Assembly; Factor 3 = immediate memory/attention--Digit Span; and Factor 4 = psychomotor speed--Coding.

The fourth factor is specific to the Coding subtest. The Coding subtest seems to have perceptual speed, memory, and motor components. While it loads with the perceptual factor in normals, it has been found to load with the memory factor among retardates. The authors suggest that the Coding subtest may be differentially affected not only by age, but also by the type of learning deficit the child has. The authors conclude that:

> This study provides at least beginning support for the possibility that a definitive clinical WISC profile for hyperkinetic children may be possible to determine (Berman & McKinney, 1973, p. 514).

Is there a relationship between the findings on psychological evaluations and those on behavioral ratings?

Gittelman-Klein and Klein (1975) investigated this question with HA children taking placebo, methylphenidate, thioridazine, and a combination of methylphenidate and thioridazine. They used a variety of behavioral ratings for teachers and parents and the following psychological test measures: WISC--11 subtests; WRAT--3 subtests; Porteus Mazes; Visual Sequential Memory (ITPA subtest); Continuous Performance Test; and Draw-a-Person Test. Behavioral ratings by parent, teacher, and physician indicated a significant global improvement over the course of the study. The psychometric measures failed to show the same degree of change. The correlational evaluation of the data indicated no relationship between psychometric and behavioral improvement after 4 weeks and a weak relationship after 12 weeks of treatment.

The authors postulate that the notion that a primary unitary, CNS function is ameliorated by the stimulants is unlikely. They suggest that drug effects are more complex. They also note that the measures presently used to assess attentional processes are far from ideal in that many functions, i.e., memory, self-rehearsal, etc., are tapped. They suggest that tests with greater construct validity for attention are necessary.

This investigation illustrates the difficulty in assessing drug effects on HA children. It raises the question of whether cognitive and behavioral patterns are

secondary "symptoms" of one dysfunction (hyperactivity) or whether they are distinct "symptoms" of separate dysfunctions. This could also explain the lack of a singular drug effect.

With our present state of knowledge, what can we then conclude about the effect of thioridazine on HA children?

Summary and Proposal

Thioridazine has been evaluated primarily in comparison to methylphenidate. Over half of the studies discussed drew conclusions about thioridazine in relation to methylphenidate. Other investigations compared thioridazine to placebo and to amphetamine in almost equal frequency. It is therefore difficult to interpret whether results are positive statements about the action of thioridazine or comparative statements indicating only an inferior position of thioridazine in relation to the stimulants.

The following statements can be made. Regarding attention span, the findings are inconsistent; there are an equal number of studies claiming significant improvement, no change, and an impairment. Concentration may or may not be affected; again results are inconsistent. Latency of response is increased, leading to an impairment in some learning tasks but reducing impulsivity. In the general category of learning abilities there is a preponderance of studies indicating a significant improvement; however, results in specific functions of attention and concentration must qualify these findings.

Few investigative evaluations have dealt specifically with thioridazine and they indicate either a beneficial change or no detectable difference.

The results on behavior ratings are inconclusive with the majority of findings indicating an improvement (i.e., reduction) in general motor activity (hyperkinesis). However, when finer discriminations are made, i.e., re social interaction and quality of behavior, thioridazine does not yield the results reported with methylphenidate.

Motor movements, measured with mechanical devices, i.e., seat movements and finger tapping, do not evidence a consistent effect. There is a tendency for no change or an impairment, i.e., slower finger tapping.

Regarding clinical evaluations of temperament and social interaction, thioridazine creates an improvement but, over time, may cause a slight deterioration in mood.

Before any clear statements can be made about the effect of thioridazine on HA children it is necessary to conduct an objective investigation comparing thioridazine to a placebo control group.

This study proposes to investigate the effect of thioridazine on two aspects of the HA pattern: the cognitive aspect of attention and motor behavior. These areas have been chosen for investigation because inattentiveness is a major problem for the HA child, and if any drug is to prove

beneficial in the management of HA children, it should affect this factor. Second, motor behavior should be affected by the tranquilizing effect of thioridazine and will serve to monitor the psychophysical effect of the drug.

<u>Hypotheses</u>

It is expected that:

1. The thiroidazine group will show an improvement of performance on posttreatment psychological measures of attention.

2. The thioridazine group will show an impairment of performance on posttreatment psychological and mechanical measures of motor coordination.

3. The Placebo group performance on posttreatment attention and motor measures will not differ from pretreatment performance.

4. The thioridazine or Drug group should be differentiated from the Placebo group on posttreatment measures of attention and motor coordination.

Within-subject changes will provide important data on individual responses to thioridazine, but group differences on posttreatment measures will provide information about the effect of thioridazine on the process of attention and the function of motor coordination in the HA child. It is the latter area which is of major importance to this investigation.

METHOD

Subjects

The subjects for this study were children between 5-1/2 and 12 years of age who had been referred to the children's unit of the Royal Ottawa Hospital for evaluation and treatment of behavioral disorders. Table 1 shows the distribution of age, sex, and IQ for the sample of 17 children.[8] All the children were considered to have moderate[9] to severe conduct and emotional problems and all but two of the children in the final sample of 14 were considered by their parents to be moderately to severely hyperactive. Table 2 shows a summary of these ratings. The Abbreviated Symptom Questionnaire (ASQ) consists of 10 items which comprise the Conners Teacher Behavior Rating Scale, and which are included in the more extensive 93-item Conners Parent Questionnaire (CPQ). Also included in the CPQ are eight items which load on the factor of hyperactivity. (See Appendix 2 for item description.) Each item is weighted according to the frequency of occurrence

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8 Three children were excluded from the final data analysis. One child was excluded because the posttreatment evaluation had been conducted as a trial run of the assessment procedure. Another child was in an accident and received a severe head injury, and the third child was discontinued on the medication at the discretion of the psychiatrist and parents.

9 See Table 2 for explanation of terms.

Table 1

Age, Sex, and IQ of Sample

Subjects	Age	IQ	Sex		
Treatment Drug					
1	5-6	125	F	Age Range	5-6 - 10-2
2	6-11	87	M	*SD*	1-6
3	6-11	91	M	$\bar{X}$	8-0
4	8-6	110	M		
5	8-8	133	M	IQ Range	87-133
6	9-5	105	M	*SD*	16.5
7	10-2	115	M	$\bar{X}$	109
Placebo Control					
8	8-6	101	M	Age Range	8-6 - 11-11
9	8-9	123	M	*SD*	1-5
10	8-11	119	M	$\bar{X}$	10-2
11	10-11	94	M		
12	11-2	95	M	IQ Range	94-136
13	11-11	109	M	*SD*	15.7
14	11-4	136	M	$\bar{X}$	111
15	6	125	M	Overall $\bar{X}$ Age	9-1
16	7	115	M	Overall $\bar{X}$ IQ	110
17	8	99	F		

Table 2

Results of Conners Behavior Rating Scale: Abbreviated Symptom Questionnaire Items; Hyperactivity Items

	ASQ				HA	
	Teacher		Parent		Parent	
Subjects	Pre	Post	Pre	Post	Pre	Post
Drug Treatment						
1*	6.7	16.7	46.7	50.0	45.8	41.7
2	36.7	23.3	60.0	23.3	70.8	45.8
3	16.7	33.3	86.7	96.7	95.8	95.8
4	53.3	83.3	63.3	93.3	58.3	75.0
5	70.0	30.0	76.7	40.0	50.0	33.3
6*	3.3	13.3	36.7	33.3	29.2	33.3
7	83.3	80.0	80.0	56.7	45.8	25.0
Placebo Control						
8	40.0	20.0	70.0	40.0	66.7	45.8
9	46.7	36.7	66.7	70.0	58.3	62.5
10	80.0	26.7	50.0	13.3	33.3	8.3
11	96.7	73.3	63.3	60.0	45.8	20.8
12	83.3	80.0	26.7	36.7	20.8	37.5
13	76.7	23.3	70.0	56.7	62.5	54.2
14	16.7	16.7	90.0	60.0	41.7	12.5

*Indicates subjects who scored less than 50% on the pretreatment behavior questionnaires.

Low = 0-29%; Moderate = 30-49%; High = 50-74%; Severe = 75-100%. These are descriptive categories arbitrarily chosen by the present author. The terms do not necessarily reflect the parents' or psychiatrists' opinion of the children.

of that behavior. For example, a behavioral statement which does not apply is weighted 0; if it applies seldom (just a little), it is weighted 1; if it describes the child as he is "very much" of the time, it is weighted 3. A per cent is then calculated based on the highest possible score. A normal child might score from 0 - 30% on the ASQ or HA factor. The items in the ASQ have been selected as those which differentiate normal children from children in an outpatient population. The HA items are descriptive of HA children. The items are also sensitive indicators of drug effects. As Table 2 indicates, all subjects scored moderately (30 - 49%) on at least one of the pretreatment ratings (either parent, teacher, or both) and all but two of the children scored high (50 - 74%) on the same pretreatment ratings. The subjects are a representative cross-section of the HA child population. Psychiatric diagnosis was that of behavior disorder with HA the major presenting characteristic for each child. One child had a learning disability as well as being hyperkinetic, and another child had a serious problem of emotional immaturity with hyperkinesis. Children diagnosed by the psychiatrist as psychotic, epileptic, or brain-damaged were excluded from the study. Also excluded were: (1) those children suffering from severe central nervous system depression; (2) children with a history of hypertensive or hypotensive heart disease of extreme degree;

(3) children exhibiting symptomatic cardiovascular disease; (4) children with a known hypersensitivity to Mellaril or other phenothiazines; and (5) children unable or unwilling to ingest tableted medication.

Apparatus

A battery of psychological tests measuring aspects of attention and motor control was individually administered to each child. Table 3 lists all the measures used in the course of the study. The initial 2-hour test battery was comprised of a complete Wechsler Intelligence Scale for Children (WISC) and Wide Range Achievement Test (WRAT) as well as the other measures. The WISC and WRAT were administered primarily for descriptive purposes so that the general intelligence level of the sample was known and any children with a learning disability would be identified. The attention and motor measures were administered twice to each child, once at the beginning of the study and again six weeks later. A full description of each measure can be found in Appendix 3.

Procedure

The children were randomly assigned to a Drug or Placebo group on the basis of consecutive precoded medication envelopes. All medication envelopes were prepared by Sandoz

Table 3

Measures Used Before and During Medication

<u>Psychological Attention Measures</u>

1. Digit Span (WISC subtest)
2. Mazes (WISC subtest)
3. Knox Cubes
4. Visual Closure (ITPA subtest)

Matching Familiar Figures

5. Reaction Time
6. Error

Continuous Performance Test

7. Number Correct
8. Commissions
9. Omissions

<u>Psychological and Mechanical Motor Measures</u>

10. Dynamometer - Grip Strength
11. Finger Tapping
12. Coding (WISC subtest)*

Grooved Pegboard

13. Drops
14. Performance Time

<u>Descriptive Measures</u>

Wechsler Intelligence Scale for Children (WISC)
- Full Scale
- Verbal
- Performance

Wide Range Achievement Test (WRAT)
- Reading
- Spelling
- Arithmetic

*See Berman and McKinney (1973).

Manufacturers such that active and placebo medications were randomized in blocks of 10. Each child as he was admitted into the study was assigned an envelope; the first child the first envelope, the second child the next envelope, and so on. Each envelope contained enough medication for the 6-week treatment phase. Information as to whether medication was active or placebo was in a sealed envelope that was to be opened only in the event of an emergency or adverse reaction necessitating identification of the medication for the welfare of the child. The standard procedure adopted was to break the seal upon completion of the eighth week of the study.

The parents and teacher completed the Conners Behavior Rating Scale as each child was admitted into the study. The child then entered a 2-week placebo washout period. The child was removed from all other medications and administered one, increasing to three, placebo tablets per day for the 2-week period. At the end of the 2-week period, the child was evaluated with the psychological test battery.

At week 3, the treatment phase began and the study medication prepared by Sandoz was administered. It was at this point that one-half (7) of the children would continue on placebo medication and one-half (7) would begin taking Mellaril. The dosage level was determined by the psychiatrist

on a ratio of 3.0 mg/kg of body weight per day as the maximum dose level. For a typical child in the study, the medication range would be as follows: week 3--three pills a day = 30 mg Thioridazine, increasing by week 4 to four pills a day = 40 mg Thioridazine, to week 5--five to six pills a day = 50 - 60 mg Thioridazine. Such that at the fifth week a child was at the maximum dose level for his body weight (approximately 40 kg or 88 pounds). He would remain at this dose level up to week 8. All envelope medication was administered in this manner so that children on placebo medication were also expected to be taking five to six pills a day by the fifth week. During the final week, the child was re-evaluated with the psychological test battery. The parents and teachers completed the Conners Behavior Rating Scale again at this time. Further information on medication protocol can be found in Appendix 4.

RESULTS

The battery of psychological measures was administered prior to the treatment phase of the study (at week 2) and again during week 8 of the study. Fourteen scores (see Table 3) were obtained for each child on both administrations. These scores were divided into two major factors: an attention factor and a motor factor. Each of these groups was further subdivided according to the direction of change in score predicted by the hypotheses. For example, an improvement in attention would be indicated by an _increase_ in reaction time (RT) on Matching Familiar Figures (MFF) and by a corresponding _decrease_ in error on the MFF.

The following subgroups were formed:

Psychological Attention Measures (improvement)

Increasing scores: Digit Span, Mazes, Knox Cubes, Visual Closure, MFF RT, CPT number correct

Decreasing scores: MFF error, CPT commissions and omissions

Motor Measures (impairment)

Increasing scores: Grooved Pegboard drops, performance time

Decreasing scores: Grip Strength, Finger Tapping, Coding

_Z_ score transformations were then calculated, and the subgroupings above were formed for each treatment group (Drug and Placebo). Four sum _z_ scores were then obtained for each subject. Figures 1 through 4 illustrate

the obtained sum Z scores on pretreatment and posttreatment administrations. The group means of these scores are shown in Table 4.

Analysis of variance (2-factor with repeated measure, fixed effects model) was computed for each measurement subgroup. The results are shown in Tables 5 and 6. The absence of a significant effect from the analyses of these measures indicates that the drug had no differential effect on any of the psychological measures. All variance can be attributed to variability among subjects.

The Conners Behavior Rating Scale also failed to clearly differentiate the Placebo subjects from Drug subjects. The teachers, however, tended to view the majority of Placebo subjects improved, while the Drug subjects were seen as unchanged. (A change in score of 15% or more was the criterion applied.) Table 6 illustrates the results of the posttreatment ratings.

Table 4

Sum Z Score Group Means

Attention Measures

I. Digit Span, Mazes, Knox Cubes, Visual Closure, MFF RT, CPT correct

Group	Time	Mean	Group	Time	Mean
Placebo	Pre	0.07	Drug	Pre	-0.28
	Post	0.73		Post	-0.52

II. MFF errors, CPT commissions, omissions

Group	Time	Mean	Group	Time	Mean
Placebo	Pre	0.40	Drug	Pre	0.01
	Post	-1.19		Post	0.78

Motor Measures

III. Grooved Pegboard drops, performance time

Group	Time	Mean	Group	Time	Mean
Placebo	Pre	-0.78	Drug	Pre	0.48
	Post	-0.49		Post	0.78

IV. Coding, Grip Strength, Finger Tapping

Group	Time	Mean	Group	Time	Mean
Placebo	Pre	0.48	Drug	Pre	-1.03
	Post	1.23		Post	-0.68

Table 5

Analysis of Variance (2-factor with Repeated Measure Fixed Effects Model) of Posttreatment Attention Measures

Source	SS	df	MS	F
I. Digit Span, Mazes, Knox Cubes, Visual Closure, MFF RT, CPT correct				
Groups (A)	4.51	1	4.51	0.35
Treatment (B)	0.30	1	0.30	0.14
A X B	1.37	1	1.37	0.61
S:A	154.42	12	12.87	
SB:A	26.75	12	2.23	
II. MFF errors, CPT commissions, omissions				
Groups (A)	4.38	1	4.38	0.48
Treatment (B)	1.19	1	1.19	1.27
A X B	9.67	1	9.67	10.28
S:A	109.62	12	9.13	
SB:A	11.28	12	0.94	

Table 6

Analysis of Variance (2-factor with Repeated Measure Fixed Effects Model) of Posttreatment Motor Measures

Source	SS	df	MS	F
III. Grooved Pegboard drops, performance time				
Groups (A)	11.25	1	11.25	2.31
Treatment (B)	0.61	1	0.61	0.56
A X B	0.00	1	0.00	0.00
S:A	58.38	12	4.86	
SB:A	13.09	12	1.09	
IV. Coding, Grip Strength, Finger Tapping				
Groups (A)	20.44	1	20.44	2.25
Treatment (B)	2.11	1	2.11	2.58
A X B	0.28	1	0.28	0.34
S:A	109.09	12	9.09	
SB:A	9.82	12	0.82	

Table 7

Perceived Change in Behavior on Conners Behavior Rating Scale*

	Teacher		Parents			
	ASQ items		ASQ items		HA items	
	Placebo	Drug	Placebo	Drug	Placebo	Drug
Improved	4	1	4	3	4	3
Unchanged	3	4	3	3	2	3
Worse	0	2	0	1	1	1

*The figures represent the number of subjects in each category.

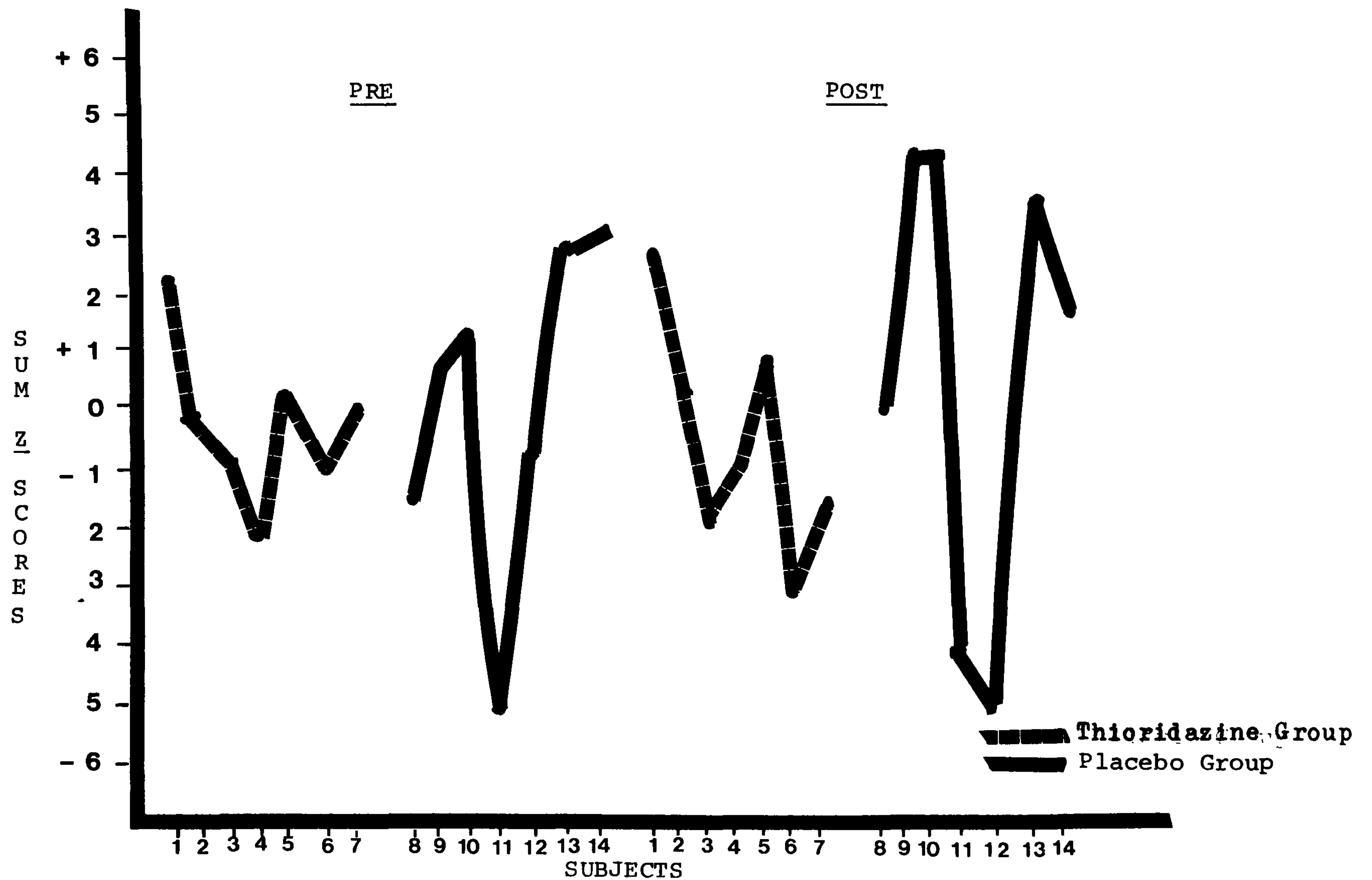

Figure 1. Sum Z Scores of the Following Attention Measures: Digit Span (WISC), Mazes (WISC), Knox Cubes, Visual Closure, MFF (Reaction Time), CPT (Number Correct).

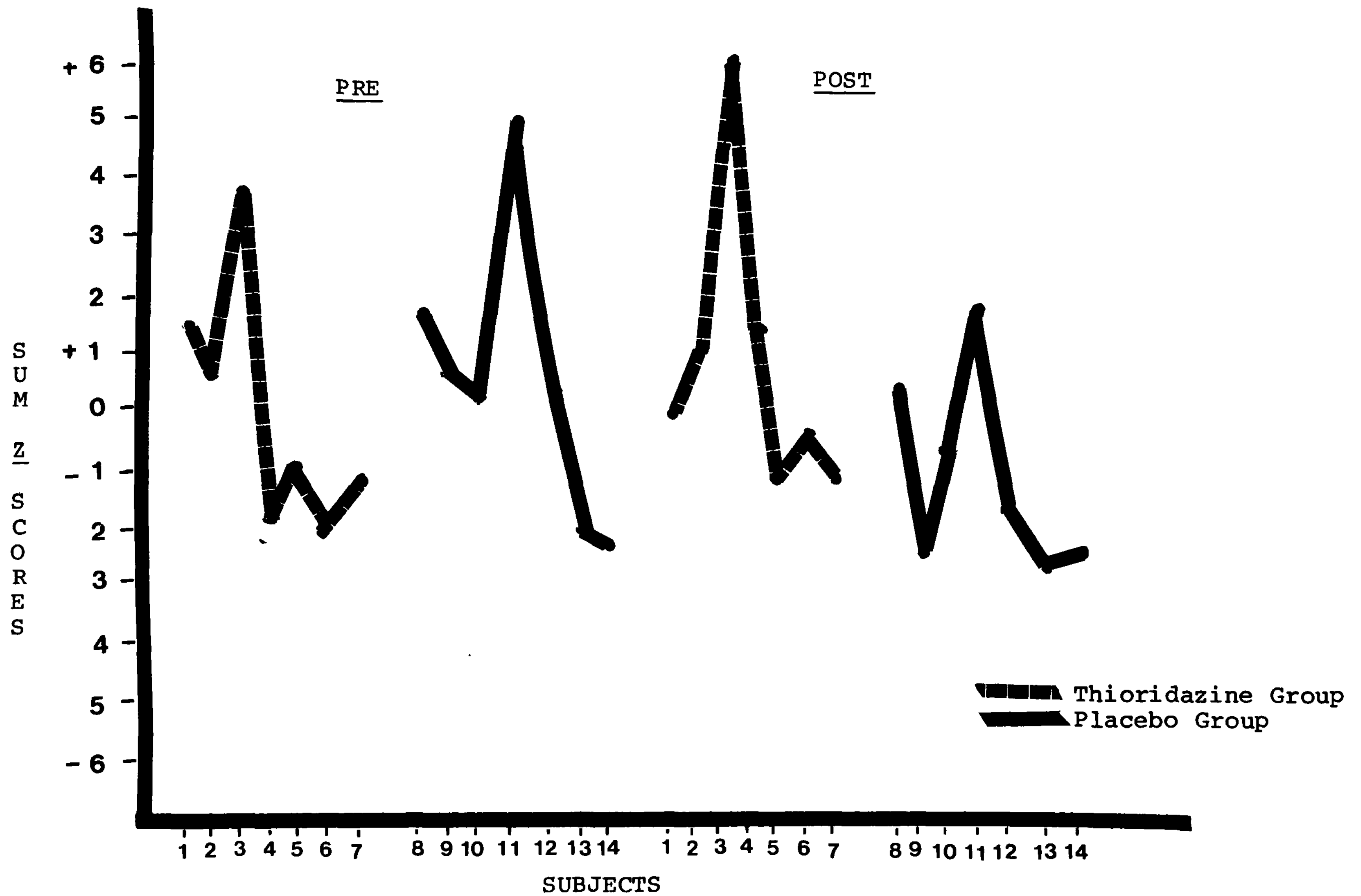

Figure 2. Sum Z Scores of the Following Attention Measures: MFF (Error), CPT (Commissions, Omissions).

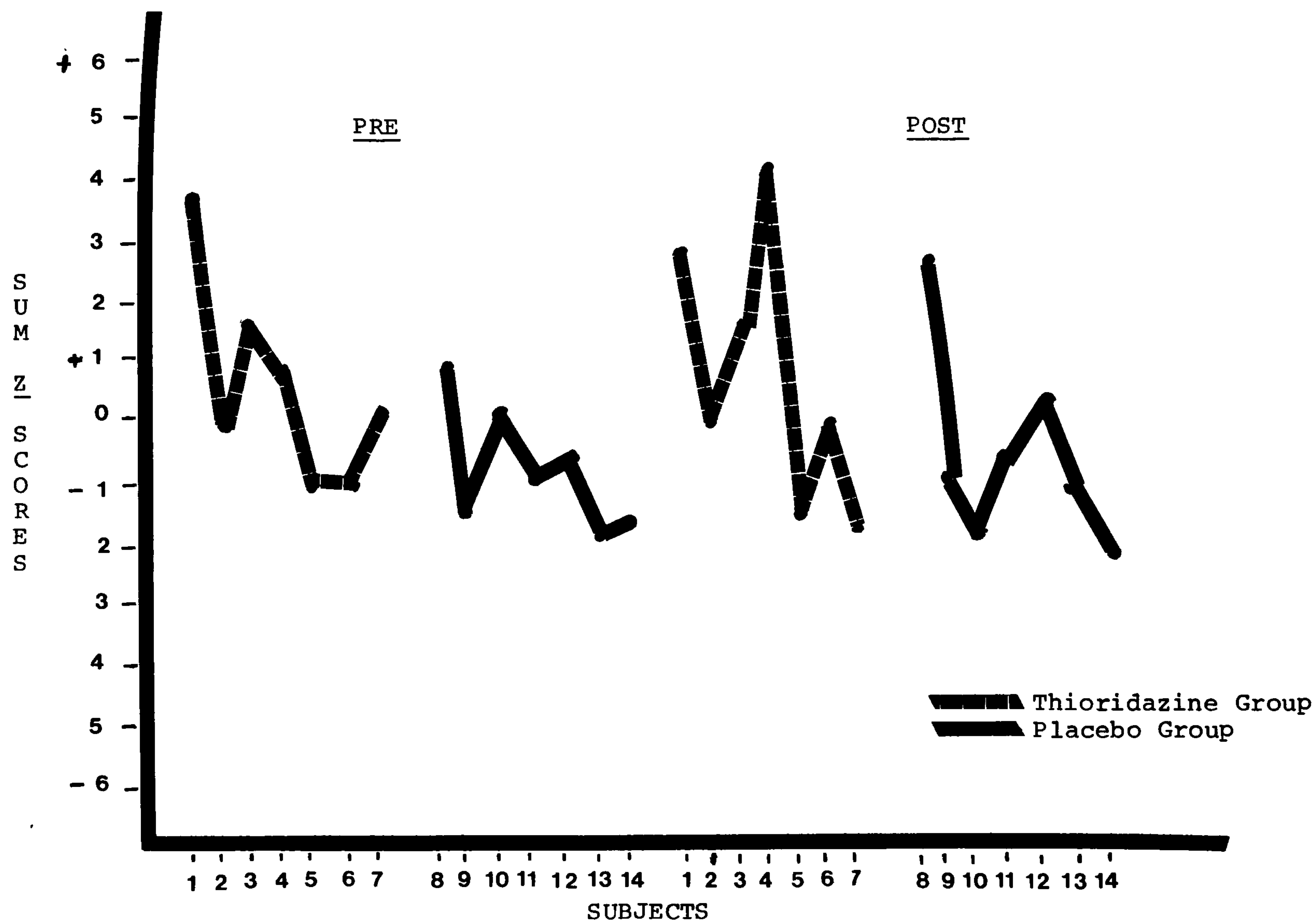

Figure 3. Sum Z Scores of the Following Motor Measures: Grooved Pegboard (Drops, Performance Time).

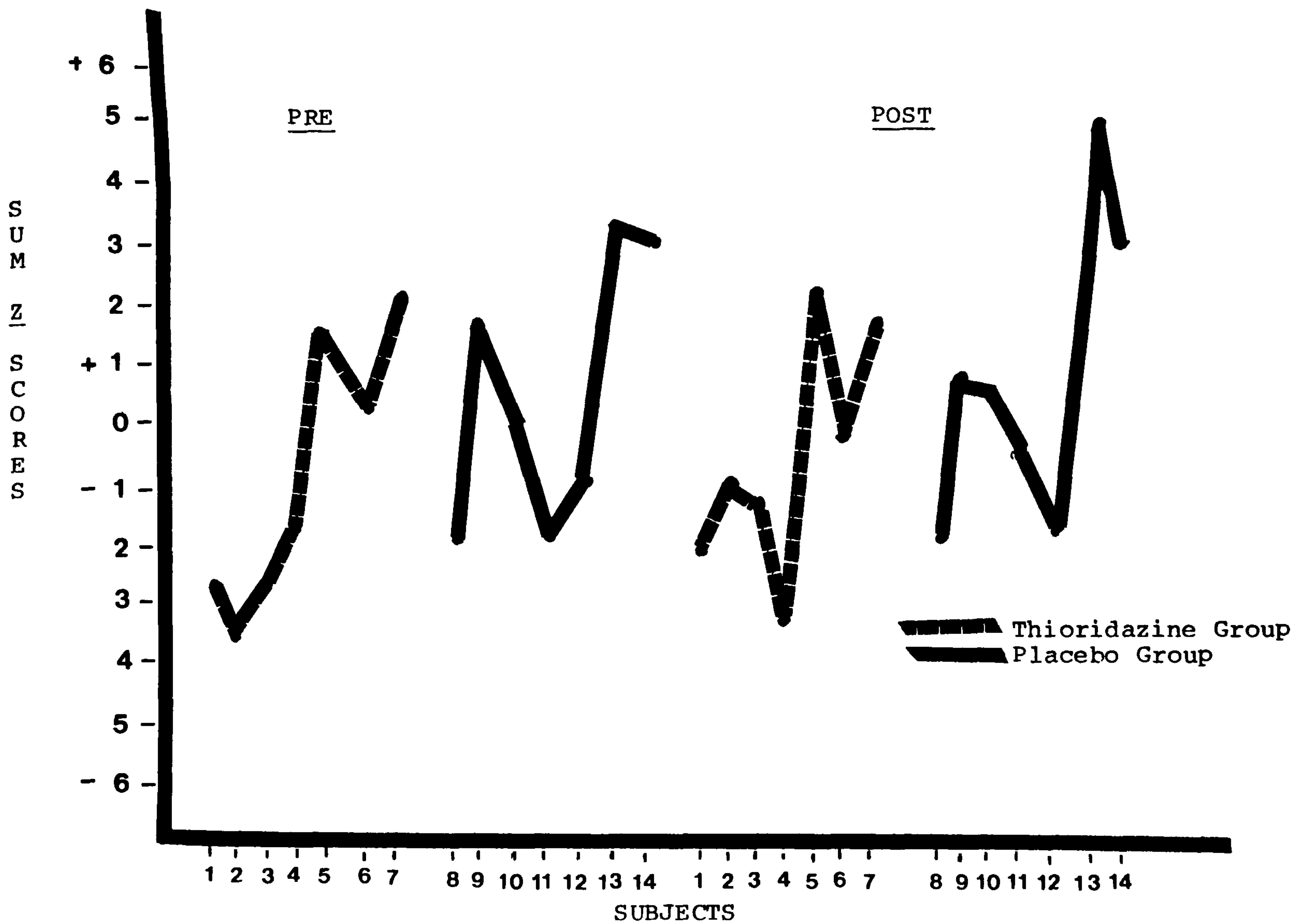

Figure 4. Sum Z Scores of the Following Motor Measures: Grip Strength, Finger Tapping, Coding (WISC).

DISCUSSION

The hypotheses are not supported by the results (with the exception of hypothesis 3, which simply expects placebo posttreatment and pretreatment data to be unchanged). There was no apparent improvement on the attention measures and no apparent impairment on the motor measures. The results of this study add to the body of research which indicates that thioridazine does not have a demonstrable effect on attention and motor behavior. Reports of favorable results on attention measures should be scrutinized in keeping with the present findings. Statements about the detrimental motor effects induced by thioridazine should also be put into perspective as this research study failed to demonstrate such an effect.

The dosage level employed was the maximum level recommended to be safe and it allowed for direct comparison among children. Proper precautions were taken to washout the effects of prior medication and the 6-week treatment phase is the standard period in which to observe optimum effect with phenothiazines. The results, then, are not spurious artifacts of an inadequate dosage. If one considers the dose-response curves postulated by Sprague and Sleator (1976) one would expect that the cognitive (attention) measures would not be improved to any great extent

at the maximum dose level. (This is not to be confused with an optimum titrated level where medication is increased till side effects occur--the maximum dosage is a standard recommended for all children and is therefore usually lower than a titrated level.) However, on the same dose-response curve one would expect a considerable improvement in social behavior for the maximum dosage. This is not the case. There were more children in the Drug group judged "unchanged" than in either of the other categories ("improved" or "worse"). It appears that the Sprague-Sleator dose-response curve does not hold for this phenothiazine.

Considering the small sample employed in the study, there were few of the confounding factors which are often associated with samples of this size. Referring to Table 1, it can be seen that the children were matched according to the age of the subject prior to data analysis to reduce any discrepancies introduced by this factor. (Several of the measures employed had standard scores which take into consideration the factor of age.) The IQ distribution was almost identical for each group and behavioral ratings were also comparable.

The failure to find posttreatment group differences is therefore not confounded by any known initial group differences. The lack of individual changes (see Figures 1 - 4) suggests that increasing the sample size would not lead to different conclusions.

Is attention a unitary factor? The answer to this question may lead to a new understanding of the present findings.

The measures employed here are frequently included in other investigations of attention (cognition) in HA children. They include a cross-section of laboratory measures (CPT & MFF) and standard clinical measures (Knox Cubes, etc.). Gittelman-Klein and Klein (1975) made the following statement on this matter:

> The measures purported to assess attentional processes are far from ideal: they are contaminated by requirements for memory, self-rehearsal, discrimination, the performance of a motor act, etc. For adequate resolution of the relationship of attentional defects to other symptoms of hyperkinetic children, tests with greater construct validity for attention are required (p. 196).

The situation regarding motor measures is less controversial, but they too are not "pure" measures (i.e., Coding).

What this discussion ultimately leads to is a resolution of the question: should research be pure and theoretical, or should it be pragmatic?

When one considers Sprague and Werry's (1970) comments, that drugs act in a multivariate situation where most of the variance is due to individual differences, environmental effects, and error of measurement not the drugs, one wonders what application can be made from research in which measures of attention have been decontaminated to yield pure psychophysical results. Should we not be evaluating drug effects in social-learning contexts by the standards available, to determine their value in treating the HA child? It has been shown that teachers' ratings of improvement in social behavior often do not correlate with findings on psychometric measures (5, 26, 64). Should psychometric measures be abandoned? No. The information which is obtained from teachers' ratings does not describe the whole child, and neither do psychometric evaluations. The value in applying present measures to determine the efficacy of Mellaril or any other drug is that the process of attention _is_ a factor in the measures, and it is reasonable to assume that the attentional process in the child is multifaceted in its expression. It should therefore be tapped by the measures available (although refinements are not unwarranted). Pure measures will yield valuable information about psychophysical properties of medication, but it is my opinion that clinical research should be more concerned with demonstrated behavioral and clinical effects of drugs.

Thioridazine failed to demonstrate any effect in the areas of attentional processes, motor control, or social behavior. It is therefore felt that despite present controversy over the lack of purity of our present measures, one can conclude that thioridazine at present does not have a demonstrable efficacy in the treatment of the HA child. At this juncture it may be more appropriate to determine what other areas of child behavior are affected by thioridazine or to determine more precisely its psychophysical properties so that there is greater theoretical soundness in its application to treating certain disorders.

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APPENDIX 1

CHEMICAL STRUCTURE OF THIORIDAZINE

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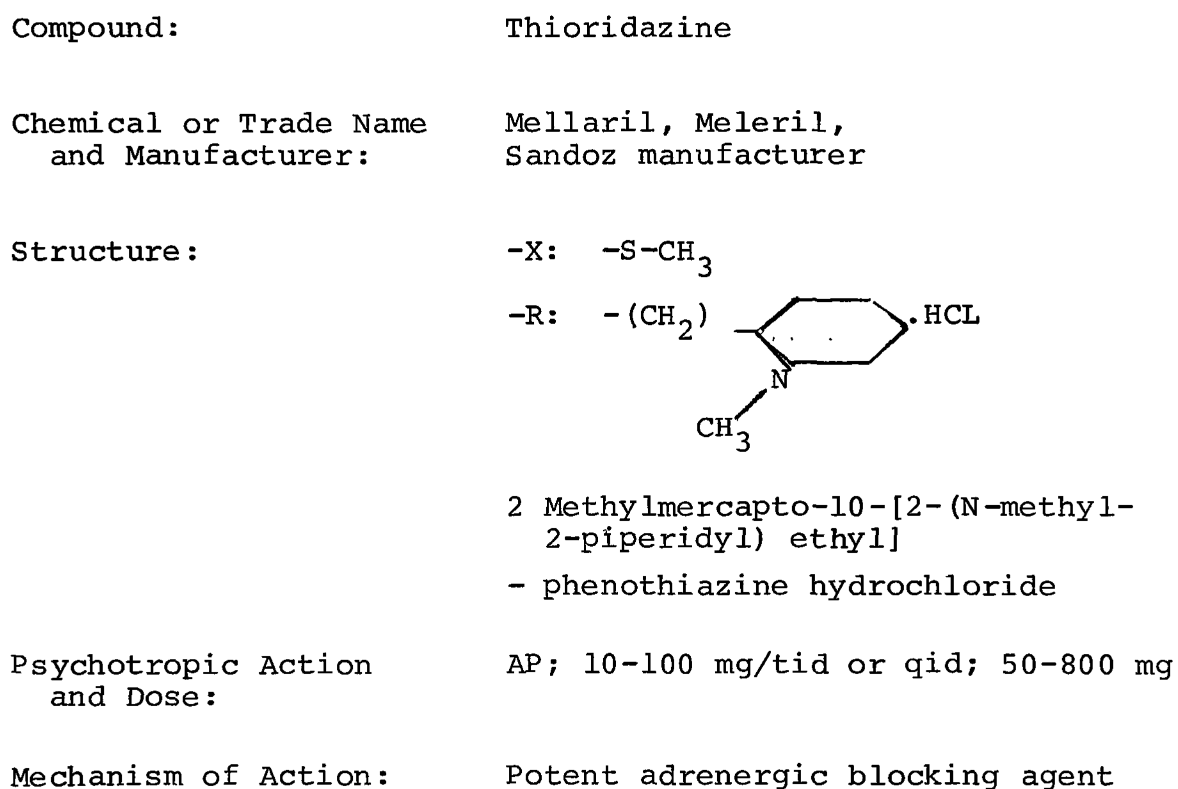

Compound: Thioridazine

Chemical or Trade Name and Manufacturer: Mellaril, Meleril, Sandoz manufacturer

Structure:

-X: $-S-CH_3$

-R: $-(CH_2)$ [piperidyl ring] .HCL

2 Methylmercapto-10-[2-(N-methyl-2-piperidyl) ethyl]
- phenothiazine hydrochloride

Psychotropic Action and Dose: AP; 10-100 mg/tid or qid; 50-800 mg

Mechanism of Action: Potent adrenergic blocking agent

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1 Adapted in part from Table I. The Pharmacological Basis of Therapeutics (3rd ed.), Goodman and Gilman, 1969, p. 205.

APPENDIX 2

CONNERS BEHAVIOR RATING SCALE ITEMS

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Abbreviated Symptom Questionnaire Items

1. Restless or overactive
2. Excitable, impulsive
3. Disturbs other children
4. Fails to finish things he starts - short attention span
5. Constantly fidgeting
6. Inattentive, easily distracted
7. Demands must be met immediately - easily frustrated
8. Cries often and easily
9. Mood changes quickly and drastically
10. Temper outbursts, explosive and unpredictable behavior

Hyperactivity Items of Parent Rating Scale

1. Inattentive, easily distracted
2. Constantly fidgeting
3. Cannot be left alone
4. Always climbing
5. A very early riser
6. Will run around between mouthfuls at meals
7. Unable to stop a repetitive activity
8. Acts as if driven by a motor

All items are check marked in one of the following categories:

	Not at all	Just a little	Pretty much	Very much
Wt.	0	1	2	3

Maximum raw score on ASQ = 30
HA = 24

APPENDIX 3

PSYCHOLOGICAL TEST BATTERY

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PSYCHOLOGICAL TEST BATTERY

Attention Measures

The Continuous Performance Test (CPT) is a test of attention and short-term memory. It consists of a set of 70 slides, each with an alphabetical letter on it, projected onto a screen in a continuous series. The subject is required to monitor the letters as they appear and depress a button each time the letter X follows the letter A. The exposure time for each slide is 0.3 seconds and the inter-trial interval is 1.7 seconds. There are 12 target stimuli. Errors of omission, commission, and correct responses are manually recorded by the experimenter. The CPT has proven to be drug sensitive and studies indicate that hyperactive children detect fewer signal stimuli at a slow interstimulus interval (approximately 1.5 seconds) (54).

Knox Cubes is an attention and short-term memory task. It consists of four small wooden cubes attached to a strip of wood. The experimenter taps the cubes in a specified order and the child is required to repeat the sequence. No latency or long-term memory component is involved. The child taps out the sequence immediately after the experimenter is finished. The sequences get progressively longer and more complex.

Matching Familiar Figures (MFF) is used to measure reflectivity, impulsivity. It is reasonable to assume that hyperactivity and impulsivity are related as Campbell found that HA children made more errors and had significantly shorter response latencies on the MFF (55). The task involves being able to select from six variants the one stimulus that is identical with the standard. This involves being able to think over alternative responses which are simultaneously available, sustain attention to the task, and not react impulsively to the stimuli.

Digit Span (WISC) requires the child to repeat a sequence of numbers immediately upon hearing the complete sequence.

Mazes (WISC) measures visual discrimination and ability to plan ahead. It consists of paper-and-pencil mazes of varying complexity (timed task).

The Visual Closure subtest of the Illinois Test of Psycholinguistic Ability (ITPA) measures the subjects' ability to discriminate figure from ground. The test consists of several long strips of paper with a picture of an animal, i.e., a dog, at the beginning of the strip. The subject is then asked to find as many dogs as he can in the remainder of the strip (timed task).

Motor Measures

Coding (WISC) has been included with motor measures because of the findings of Berman and McKinney (1973) in a factor analysis of the WISC scores obtained from HA children. The task involves copying marks or numbers from a sample to rows below (timed task).

Finger Tapping involves tapping the index finger on a mechanical device while the remainder of the hand is flat on the table. The taps are mechanically counted (timed task).

Grip Strength measures the subjects' grip with a dynamometer.

The Grooved Pegboard consists of a small metal tray with rows of holes and tiny metal pegs. The subject is required to place as many of the pegs in the holes as he can, using one hand, not skipping any holes, and working by rows. The time it takes to complete two rows is recorded.

APPENDIX 4

STUDY MEDICATION PROTOCOL

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STUDY MEDICATION PROTOCOL

Permission

Since all children entering this study were under age 18, their representatives (parents, guardians) were informed that drugs were being used for investigational purposes and were advised of the potential benefits as well as potential adverse effects of medication therapy. Parents/guardians were further advised that they could withdraw their child from the study at any time. Upon the approval of the parent/guardian, written consent was obtained before any subject was entered into the study.

Study Medications

Study medication was prepared by Sandoz as follows:

1. Thioridazine, 10 mg tablets

Each Mellaril 10 mg tablet contains: Thioridazine HCl, U.S.P. 10 mg, Calcium Sulfate, N.F. .105 gm., Stearic Acid .003 gm., Keltose .007 gm., Starch, U.S.P. .005 gm, Lactose, U.S.P. .0247 gm, Gelatine, U.S.P. .0003 gm, Acacia, U.S.P. .00125 gm, Talc, U.S.P. .00776 gm, Sucrose, U.S.P. .0359 gm.

2. Placebo for Mellaril, 10 mg tablets containing inactive ingredients only

Each placebo for Mellaril tablet contains: Calcium Sulfate, N.F. .015 gm, Stearic Acid .003 gm, Keltose .007 gm, Starch, U.S.P. .005 gm, Lactose, U.S.P. .0347 gm, Gelatin U.S.P. .0003 gm, Acacia, U.S.P. .00125 gm, Talc, U.S.P. .00776 gm, Sucrose, U.S.P. .0359 gm.

The coating for all tablets (active and placebo) contains: Opalux Suspension Q.S.A.D., Carnauba Wax .00004 gm, Markem Ink #2200 A/L Med.Cer.Blue Q.S.A.D.

Concomitant Medication

No other major or minor tranquilizer, antidepressant, stimulant, or sedative was administered during the study.

Antihypertensive drugs such as reserpine and pargyline, which have potent psychotropic action in addition to their main effects, were prohibited during the course of the study.

Other medications which were considered necessary for the child's welfare were given at the discretion of the psychiatrist.

Adverse Reactions

All adverse reactions occurring during the study were reported. If a child developed side effects as the dose was increased, then the dose was reduced to the level

of stabilization for the remainder of the study. This was the only condition in which the psychiatrist was no longer blind to the source of medication. At no time, however, was the experimenter made aware of medication levels, so all psychological evaluations were conducted in a blind manner.